Ebf1 and c-Myb repress rag transcription downstream of Stat5 during early B cell development.

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Authors: Greg A Timblin, Mark S Schlissel

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Public Summary:
The generation of diverse B and T cell antigen receptor repertoires during early lymphocyte development is dependent on the gene recombination activity of the Rag proteins. As B and T lymphocytes develop, the balance between proliferation and differentiation, along with the expression of Rag during specific parts of the cell cycle, must be tightly regulated to maintain genomic integrity and ensure the production of diverse pools of B and T cells. In this study, we used Abelson murine leukemia virus transformed B cell lines to identify novel pathways and factors responsible for the repression of Rag transcription at a specific point in B cell development. We demonstrated that the transcription factor early B cell factor 1 (Ebf1) and c-Myb, positive regulators of Rag transcription during early B cell development, function as repressors of baseline Rag expression at this later stage. In this context, Ebf1 and c-Myb act downstream of the signaling molecule Stat5 to repress differentiation and promote proliferation and survival of transformed cells. Ebf1 and c-Myb represent attractive therapeutic targets in hematopoietic malignancies such as acute lymphoblastic leukemia.

Scientific Abstract:
The temporal control of RAG (Rag) expression in developing lymphocytes prevents DNA breaks during periods of proliferation that could threaten genomic integrity. In developing B cells, the IL-7R and precursor B cell Ag receptor (pre-BCR) synergize to induce proliferation and the repression of Rag at the protein and mRNA levels for a brief period following successful Ig H chain gene rearrangement. Whereas the mechanism of RAG2 protein downregulation is well defined, little is known about the pathways and transcription factors that mediate transcriptional repression of Rag. Using Abelson murine leukemia virus-transformed B cells to model this stage of development, we identified early B cell factor 1 (Ebf1) as a strong repressor of Rag transcription. Short hairpin RNA-mediated knockdown of either Ebf1 or its downstream target c-Myb was sufficient to induce Rag transcription in these highly proliferative cells. Ebf1 and c-Myb antagonize Rag transcription by negatively regulating the binding of Foxo1 to the Rag locus. Ebf1 accomplishes this through both direct negative regulation of Foxo1 expression and direct positive regulation of Gfi1b expression. Ebf1 expression is driven by the IL-7R downstream effector Stat5, providing a link between the negative regulation of Rag transcription by IL-7 and a novel repressive pathway involving Ebf1 and c-Myb.